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HEREDITARY DISEASES OF THE EYE RESULTING IN BLINDNESS. THEIR SOCIAL CONSEQUENCES. THE MEASURES THAT MAY BE PROPOSED

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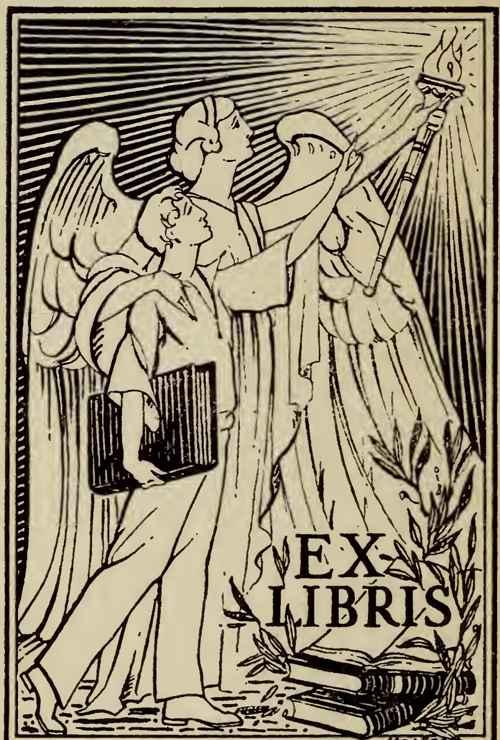
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OPENING REPORT
HEREDITARY DISEASES OF THE EYE RESULTING IN BLINDNESS; THEIR SOCIAL CONSEQUENCES; THE MEASURES THAT MAY BE PROPOSED.[1]

by Prof. A. FRANCESCHETTI (*Geneva*)

As the question of heredity in ophthalmology has occupied me for many years, I was pleased to accept the invitation extended to me in September 1934 by the Committee of the International Association for the Prevention of Blindness, to present a paper on the hereditary diseases of the eye leading to blindness. I had no illusions, however, about the difficulties that would arise in attempting to present a complete discussion; difficulties due, on the one hand, to the relatively short time at my disposal (all those who have occupied themselves with the question, are familiar with the difficulty of choosing from the enormous mass of ophthalmological literature those researches which permit one to draw definite conclusions), and due, on the other hand, to the extreme paucity of statistics regarding the questions that interest us here, paucity to which I shall have occasion to refer in the following.

Before continuing, I wish to thank the members of the Commission of the International Association for the Prevention of Blindness who were kind enough to lighten my task in communicating their personal observations to me, and in calling my attention to valuable sources.

I am particularly grateful to Dr. Waardenburg, of Arnhem,

(1) Translated from the French by Abraham S. Haft, B. Sc.

and to Prof. Fleischer, of Erlangen, who have provided me with detailed reports from which I have drawn considerable information.

Dr. Park Lewis, of Buffalo, has very obligingly placed abstracts of the American literature at my disposition; literature which is generally difficult to obtain in Switzerland. I also wish to thank Professors Terrien and van Duyse and Mr. Usher for the interesting information they have given me.

I. — THE HEREDITY OF EYE DISEASES

The eye especially lends itself to researches in heredity, because it is possible to observe the hereditary anomalies directly, and very often to measure their dimensions. It is for this reason that there exists to-day a vast and detailed literature on hereditary diseases in ophthalmology. These researches concern themselves above all with pedigrees, for it is primarily the familial appearance of these affections which has interested the various observers. It is thus that we have learnt the mode of transmission in the greater number of eye diseases due to a modification of the idioplasm. The isolated cases of these eye diseases, however, have been neglected almost to the present day. The result is that our knowledge of the number of single-case pedigrees is almost nil despite the innumerable statistical studies, and that we also know very little about the descendants of these patients.

A. — The mode of transmission of the various eye diseases

Our knowledge of the mode of transmission of the various eye diseases is based, as we have just seen, on the researches on their familial appearance, and upon the study of the pedigrees.

Nettleship was the first to publish detailed pedigrees in ophthalmology. His pedigree of dominant night-blindness is still the most important. It was as the collaborator of Nettleship that Usher undertook the publication of an extremely interesting series of genealogical trees, which may serve as examples to all investigators. His pedigrees give very precise information concerning all the members of a

family, not only about those with eye diseases, but also about those who are well, or who are suffering from other affections. Usher has also published equally detailed single-case pedigrees.

The interest in human heredity since the beginning of the century is largely the result of the rediscovery of the Mendelian laws by Correns, de Vries, and Tschermak in 1900.

Davenport (1908), Lutz (1911), and Steiger (1913) are responsible for the application of these laws to ophthalmology.

We now possess a long series of complete investigations of heredity in ophthalmology. They may be listed, in chronological order, as follows :

Grœnouw (1920),
Clausen (1924-25),
Fleischer (1929),
Franceschetti (1930),
van Duyse (1931),
Waardenburg (1932).

We have in addition a very complete bibliography by Howe (1921-1928). We must not overlook the work of Julia Bell. In five volumes of the great encyclopedia, " The Treasury of Human Inheritance ", edited by Karl Pearson, she has summarized our present knowledge of certain affections of the eye (retinitis pigmentosa, congenital night-blindness, glioma, colour-blindness, blue sclerotic and fragility of bone, Leber's disease, glaucoma), and illustrated it with all the pedigrees known to date.

In man, as in animals, the normal characters depend upon a considerable number of genes (polygenetic). The human race, however, is not prolific, and it is almost impossible to determine the genotype of the individual.

It is established, that the hereditary pathological conditions are generally due to the modification of a single gene.

Waardenburg has very rightly insisted, however, that these hereditary diseases are not caused by the alteration of a single gene, but that, as for normal characters, the other genes play a part. It is, nevertheless, undoubtedly true, that, in general, it is sufficient that a single gene be modified for the pathological condition to appear.

The hereditary diseases of the eye are, in general, also caused by the modification of but one gene. There are, however, certain ocular affections whose mode of transmission is not in accord with the laws determined for the

inheritance of monogenetic defects. If two or three genes are modified, the determination of the genotype becomes very difficult. It has been possible to make a digenetic classification of certain ocular defects (see the following chapter).

The diagnosis of the hereditary eye diseases is simple for most of the congenital conditions. There are certain defects, however, which may be of inflammatory origin (syphilis, etc.). The post-natal ocular defects are generally more difficult to diagnose, as the inflammatory and senile affections may present identical clinical features.

The determination of the genotype becomes extremely difficult for those anomalies where the normal condition is subject to wide physiological variations (size of the cornea, refraction, etc.). It is probable that the refraction is determined by the interplay of a great number of genes. Thus in the cases of high myopia, for example, these genetic factors play such a part that it is almost impossible to determine the influence of the pathological gene or genes.

Even for the defects that are very easy to diagnose (coloboma, cataract, etc.), there are often abortive forms which would pass unnoticed were they not discovered by the study of the genealogical tree.

We do know a considerable number of hereditary eye diseases, whose mode of transmission has been established. To make a prognosis in children whose parents or relatives are affected with hereditary anomalies, it is indispensable to know the mode of transmission of the various ocular defects which may lead to more or less complete blindness.

I have therefore esteemed it useful to summarize the mode of transmission of the various eye defects.

MODE OF TRANSMISSION OF THE VARIOUS OCULAR DEFECTS

Defect	Mode of transmission
I. — *Affections of the extrinsic muscles*	
A) Ptosis	Generally dominant.
B) Ophthalmoplegia externa	Generally dominant, sometimes recessive.
(Ptosis with epicanthus. Ptosis with blepharophymosis. Late ptosis.)	Generally dominant.
C) Nystagmus (without alteration of the fundus oculi)	i) Irregularly dominant, ii) Sex-linked recessive, iii) Simple recessive, iv) Eventually sex-linked dominant.

Defect	Mode of transmission
Nystagmus with myopia and amblyopia (Nystagmus with macular aplasia see III.)	Dominant.

II. — *Colobomata and other Homologous Affections*

A) Aniridia	Dominant.
B) Irido-choroid coloboma (Coloboma oft he macula and of the optic nerve)	Generally dominant, occasionally recessive.
C) Corectopia and Ectopialentis	
1. Corectopia	Generally dominant.
2. Congenital ectopia lentis with Marfan's disease	Generally dominant. Dominant (occasionally irregular).
3. Congenital corectopia and ectopia lentis	Recessive.
4. Post-natal dislocation of the lens	Dominant.
D) Microphacia	Recessive.
E) Microphthalmia	Dominant and recessive.
1. Microphthalmia with coloboma	Generally dominant.
2. Complicated microphthalmia	Dominant or recessive (eventually sex-linked recessive).
3. Simple microphthalmia	Generally recessive.
F) Anophthalmia	Dominant or recessive.

III. — *Defects of Pigmentation*

A) Complete universal albinism	Recessive.
B) Incomplete universal albinism	Recessive (eventually dominant).
C) Albinism of the eye	Sex-linked recessive.
D) Albinism of the fundus oculi	Sex-linked recessive.
E) Aplasia of the macula	Recessive, sex-linked recessive, (eventually irregularly dominant).
(Aplasia of the macula and retina with secondary nystagmus)	Recessive.

IV. — *Glaucoma*

A) Hydrophthalmia	Recessive.
B) Juvenile and adult glaucoma (Glaucoma with aplasia of the mesodermal layer of the iris)	Generally dominant. Sex-linked recessive.

V. — *Malignant Tumours*

Defect	Mode of transmission
A) Glioma of the retina	Probably dominant (digenetic).
B) Von Hippel-Lindau's disease	Probably dominant.
C) Xeroderma pigmentosum	Probably recessive.

VI. — *Defects of Refraction*	Generally due to several factors (polygenetic).
A) High myopia	Recessive (probably occasionally dominant or sex-linked recessive).
B) High hypermetropia	Recessive (occasionally dominant, often irregularly dominant).
C) Astigmatism	Irregularly dominant (occasionally recessive or intermediate).

VII. — *Corneal Defects*

A) Microcornea	Dominant or recessive (probably polygenetic).
B) Cornea plana	Probably recessive.
C) Megalocornea	Sex-linked recessive.
D) Macrocornea	Dominant (probably polygenetic).
E) Keratoconus	Dominant (probably digenetic).

VIII. — *Affections of the Sclerotic*

A) Blue sclerotics, fragility of bone and oteosclerosis (Van der Hoeve's syndrome)	Dominant.

IX. — *Affections of the Lens*

A) Congenital cataract	Generally dominant (occasionally irregular).
B) Zonular cataract	Irregularly dominant.
C) Juvenile, pre-senile and senile cataract	Dominant (often irregular).
D) Cataract in Dystrophia myotonica	Dominant (polygenetic).

X. — *Affections of the Retina and Optic Nerve*

A) Total colour-blindness	Recessive.
B) Colour-blindness	Sex-linked recessive.
C) Congenital night-blindness	*a*) Dominant (Nougaret type). *b*) Recessive.
Congenital night-blindness with myopia	Sex-linked recessive.

Defect	Mode of transmission
D) Cerebro-retinal abiotrophies	
1. Amaurotic family idiocy (Tay-Sachs disease)	Recessive.
2. Juvenile amaurotic idiocy (Disease of Vogt-Spielmayer)	Recessive.
E) Tapeto-retinal abiotrophies	
1. Macular family degeneration	Dominant (often irregular), eventually recessive or sex-linked recessive.
2. Retinitis pigmentosa	Generally recessive, occasionally dominant, rarely sex-linked recessive.
F) Aplasia of the retina (see III.)	Recessive ?
G) Atrophy of the optic nerve	
1. Leber's disease	
a) European form	Sex-linked recessive (the hetero zygous females are occasio nally affected).
b) Japanese form	Sex-linked recessive (the heterozygous females are very often affected).
2. Juvenile optic nerve atrophy	Dominant.
3. Congenital atrophy	Recessive, rarely dominant.
4. Optic nerve atrophy with cerebral affection (Cerebellar ataxia (P. Marie)	Dominant or recessive.
Disease of Pelizaeus-Merzbacher	Sex-linked recessive.
5. Optic atrophy and cranial malformation	Irregularly dominant.
Dysostosis cranio-facialis, oxycephaly and acrocephalosyndactyly (Apert).	Unknown.

The following table indicates the mode of transmission of the defects of the different parts of the eye. (The less frequent mode of transmission is placed in parentheses.)

TABLE I

Diseases of :	Dominant	Irregularly Dominant	Recessive	Sex-linked Recessive	Digenetic (2 dominant genes)	Sex-linked Dominant	Polygenetic or Unknown
1. *Extrinsic Muscles and Eyelids.*	Ptosis. Ophthalmoplegia. Complicated Ptosis.	Nystagmus.	(Ptosis + Ophthalmoplegia.) (Ophthalmoplegia.)	Nystagmus	Mongolian idiocy.	(Nystagmus.)	Strabismus.
2. *Cornea.*	Microcornea. Macrocornea. Family degeneration.		Microcornea. Cornea plana.	Megalocornea.	Keratoconus.		(Microcornea.) Macrocornea. Keratoconus.
3. *Sclerotic.*	Blue eye (van der Hoeve's Syndrome).						
4. *Lens.*	Congenital Cataract. Juvenile, presenile, senile, cataract. Cataract in dystrophia myotonica. Ectopia lentis. Dislocation of the lens.	(Congenital Cataract.) Zonular Cataract. Juvenile, presenile, senile, cataract. Corectopia.	Congenital Cataract. Juvenile Zonular Cataract. Ectopia lentis and Corectopia. Microphacia.				
5. *Uveal tract and entire globe.*	Aniridia. Uveal Coloboma Microphthalmia with coloboma. Complicated microphthalmia. Anophthalmia. (Cryptophthalmia.)		Uveal Coloboma Simple Microphthalmia. Complicated Microphthalmia. Anophthalmia.	Complicated Microphthalmia.			

DISEASES OF :	DOMINANT	IRREGULARLY DOMINANT	RECESSIVE	SEX-LINKED RECESSIVE	DIGENETIC (2 DOMINANT GENES)	SEX-LINKED DOMINANT	POLYGENETIC OR UNKNOWN
6. *Retina.*			Complete universal Albinism.	Albinism of the eye.			
		(Incomplete universal Albinism.)	Incomplete universal Albinism.				
				Albinism of the fundus oculi.			
		(Aplasia of the macula.)	Aplasia of the macula.	Aplasia of the macula.			
			Total colour blindness.	Colour blindness.			
	Night-blindness		Night-blindness (Oguchi's disease).	Night-blindness + myopia.			
			InfantileAmaurotic family idiocy.				
			Juvenile amaurotic family idiocy.				
	Family degeneration of the macula.	Family degeneration of the macula.	(Family degeneration of the macula).	(Family degeneration of the macula.)			
	(Retinitis pigmentosa.)		Retinitis pigmentosa.	(Retinitis pigmentosa.)			
			Aplasia of the retina ?				

Diseases of :	Dominant	Irregularly Dominant	Recessive	Sex-Linked Recessive	Digenetic (2 dominant genes)	Sex-Linked dominant	Polygenetic or Unknown
7. *Optic nerve.*	Juvenile Atrophy of the optic nerve. (Congenital atrophy of the optic nerve).		Congenital atrophy of the optic nerve.	Hereditary optic Atrophy (Leber's disease).			
8. *Glaucoma.*	Juvenile and Adult glaucoma.		Buphthalmia.	Glaucoma with aplasia of the mesodermal layer of the iris.			
9. *Refraction.*		Astigmatism.	High myopia. High hypermetropia.	(Myopia). Myopia+Night blindness			Myopia. Astigmatism. Hypermetropia
10. *Malignant Tumours.*	Von Hippel-Lindau's disease.		Xeroderma pigmentosum.		Glioma.		

B. — The mode of transmission and the prognosis for the descendants

The mode of transmission is of capital importance in the appearance of the ocular defect in the descendants. Inasmuch as the same defect may have two entirely different modes of transmission, the exact knowledge of the pedigree is indispensable in order to be able to make a precise prognosis. The probability that several descendants be affected varies with the mode of transmission. We shall therefore summarize the relationship between the mode of transmission and the dangers resulting to the offspring.

I. *Regular dominance*

We are generally concerned with a marriage between a heterozygous, and therefore diseased, individual and a normal individual. According to the Mendelian formulae 50 % of the children should be affected. The prognosis can therefore be made quite easily.

II. *Irregular dominance*

The prognosis is more difficult to make since the heterozygote may be apparently healthy. The genotypic affection, therefore, does not manifest itself, although theoretically dominant. These variations of the phenotype are particularly frequent for the colobomata. The frequence with which a normal or pathological character manifests itself in a heterozygous individual is denoted by the term penetration. Unfortunately, there are no statistics in ophthalmology which shed any light on this problem. In psychiatry, where they are more advanced, the following figures have been obtained :

Mental debility	100 %	penetration
Dementia praecox (Schizophrenia)	66 %	penetration

(quoted from Luxenburger)

The importance of irregular dominance is that the descendants of apparently healthy parents may be affected, which does not occur in regular dominance. The probability that

a descendant of an individual subject to a disease transmitted by irregular dominance be also affected is equal to half the penetration in per cent.

III. *Recessive*

A recessive defect generally manifests itself in one-fourth of the children if the two parents are heterozygous. The children of the diseased individual are generally (although all heterozygous) apparently healthy. This is only true of the relatively rare defects. For the more or less frequent anomalies, like high myopia, the number of heterozygous individuals in the population is considerable. (One per cent. of homozygous individuals corresponds to 18 % of heterozygotes in the population.) Thus, in practice, the heterozygous offspring of a diseased individual are very likely to marry another heterozygote. In this wise the defect reappears in the second generation. Moreover, if the diseased individual marries a heterozygote, 50 % of the children will be diseased.

Even for the rare recessive hereditary defects, the prognosis must be guarded. I have personally observed a case of a man affected with congenital buphthalmia from both sides, whose first child, a girl, also presented a bilateral buphthalmia despite the fact that there was no consanguinity of the parents. Scheerer has also observed a buphthalmia in father and daughter. Do we have marriage between patient and carrier, or a change of dominance ? Question which cannot be answered, but which emphasises the necessity for a guarded prognosis. Even though the children of patients affected with a recessive hereditary anomaly are generally healthy, it must be recalled that two-thirds of the brothers and sisters, and all of the children are heterozygous, and consequently transmit the altered gene to their offspring. If these offspring marry heterozygotes, the disease reappears in their children.

The danger of marriage between two heterozygotes is particularly great when the two individuals are related. Here the importance of consanguinity in the manifestation of recessive defects is plain.

The following table illustrates the importance of consanguinity; importance which increases directly with the rarity of the disease.

LENZ'S TABLE

(for 1 % of consanguineous marriages in the population)

Occurrence of patients suffering from a recessive disease whose parents are not consanguineous	Occurrence of patients suffering from a recessive hereditary disease (including descendants of consanguineous parents)	Percentage of parents who are first cousins
1 : 1		1
1 : 2		1
1 : 10		1.2
1 : 100		1.6
1 : 400		2.2
1 : 900		2.9
1 : 1,600		3.5
1 : 2,500		4.0
1 : 4,900		5.1
1 : 10,000		6.8
1 : 40,000		12
1 : 90,000		16
1 : 160,000	1 : 125,000	21
1 : 490,000	1 : 300,000	31
1 : 10^6	1 : 540,000	38
1 : 4 $\times 10^6$	1 : 1.5 $\times 10^6$	55
1 : 25 $\times 10^6$	1 : 4.6 $\times 10^6$	76
1 : 100 $\times 10^6$	1 : 10.5 $\times 10^6$	86

We have a whole series of statistics dealing with the frequency of consanguinity in recessive ocular defects, but their value is only relative inasmuch as they are concerned with a selected material and not with the entire population [see table 2]. A perfect statistical study is that of Sjoegren (1931) which shows that for Juvenile Amaurotic Idiocy the consanguinity of the parents is 25.7 $\pm$ 7.4 %.

In 106 cases of recessive hereditary eye diseases Waardenburg found 19 (21.8 %.) with consanguineous parents and 87 (70.2 %.) without consanguineous parents. As the frequency of consanguinity in Holland is approximately 1 %. in the population, one can, as Waardenburg has done, determine the probability for consanguineous and non-consanguineous marriages of having children affected with recessive eye diseases.

According to the figures mentioned, the relation is

$$\frac{78.2}{99} : \frac{21.8}{1} = 1 : 27.6$$

TABLE 2

Recessive affection	Frequency of consanguinity	Authors
Colour = blindness . . .	25-33 %	Peter, Waardenburg, Beckershaus.
Universal albinism . . .	20-33 %	Davenport, Waardenburg.
Buphthalmia	7-10 %	Zahn, Waardenburg.
Retinitis pigmentosa. . .	24-30 %	Julia Bell, Lenz, Usher, de Wilde.
Microphthalmia	23 %	Waardenburg.
Infantile amaurotic idiocy	30 % (Jews) 50-60 % (non-Jews)	Slom.
Juvenile amaurotic idiocy	25 %	Sjoegren.
Oguchi's disease.	62 %	Takagi-Kawakami.
Microphacia	27 %	Franceschetti (1).

It follows that for consanguineous marriages the probability of having children with recessive ocular defects is, according to Waardenburg, 27 times as great as for non-consanguineous marriags.

These figures are so striking in themselves that one might expect every oculist to be convinced of the importance of consanguinity as a factor in the manifestation of the hereditary eye diseases. A recent paper by Barret (1927), however, reveals that even to-day the ophthalmologists often underestimate this factor. In this paper the author recalls the importance of consanguinity in ophthalmology. He mentions the Pharaohs who for centuries married their sisters, and in whom degeneracy only manifested itself in the eighteenth generation. He concludes from this that marriage between first cousins is without danger if there are no hereditary diseases in the family. It is obvious that in an absolutely healthy family consanguineous marriages may even protect against degeneracy introduced into the family by non-consanguineous marriages. The genes recessive for general or ocular defects are, however, so widespread in the population to-day, that consanguinity must be considered dangerous, as is proven by the already mentioned figures. Moreover, it must be remembered, that the danger is not only that eye diseases, but that a number of general, and

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(1) For 11 published cases, the parents were consanguineous in 2 (Franceschetti, Waardenburg). In one unpublished case that I have observed there was consanguinity of the parents.

particularly cerebral, anomalies be manifested, given the number of pathological genes in the population. It is obvious that two heterozygotes may fortuitously marry. The chance of finding two altered genes in the same individual is, however, much greater in the offspring of consanguineous parents.

IV. *Sex-linked recessive*

For the sex-linked recessive diseases, the pathological gene is in the x-chromosome. Whereas the woman has two x-chromosomes, the man has only one, and if this chromosome is affected, the anomaly becomes manifest. According to the laws of heredity the x-chromosome of the father is transmitted to the daughter. She thus becomes a carrier in 100 % of the cases, if the chromosome is modified. If the mother is a carrier, 50 % of her daughters are also carriers, as she always transmits one of her two chromosomes to them. The sex-linked recessive hereditary diseases are therefore transmitted as follows :—

1. From the patient by his daughters to his grandsons.

2. By the sisters of the patients to their sons, or by their daughters to their grandsons.

The following figure shows the mode of transmission and the occurrence of affected individuals and carriers in the sex-linked recessive hereditary diseases.

TABLE 3

	Brothers	Sisters	Sons	Daughters	Grandsons (By the Daughters)	Grand-daughters (By the Daughters)
1. Husband diseased Wife sound.	50 % diseased	50 % carriers	sound	100 % carriers	50 % diseased	50 % carriers
2. Husband sound, Wife carrier :						
a) Father diseased.	sound	100 % carriers	50 % diseased	50 % carriers	25 % diseased	25 % carriers
b) Mother carrier.	50 % diseased	50 % carriers			(50 % if the mother is a carrier)	
3. Wife diseased (father always diseased). Husband sound	50 % diseased	50 % diseased 50 % carriers	100 % diseased	100 % carriers	50 % diseased	50 % carriers
4. Husband diseased	See 1 and 2 (a. and b.)		50 % diseased	50 % diseased	100 % diseased	100 % carriers
Wife carrier				50 % carriers	50 % diseased	50 % carriers
5. Husband diseased. Wife diseased	See 1 and 3		100 % diseased	100 % diseased	100 % diseased	100 % carriers

Variations 1 and 2 in the above table are the most important, whereas variations 3, 4, and 5 are very rare, especially for the serious hereditary defects. Examples concordant with the theory have been observed for colour-blindness.

The observations on colour-blindness in man are most in accord with the theory. For the serious sex-linked anomalies, there are a certain number of exceptions, the knowledge of which is essential for the prognosis of the heredity. These exceptions are :

1. *Manifest heterozygotism.*

According to the theory, the carriers of sex-linked hereditary anomalies must be outwardly healthy. There are, however, exceptions to this rule in certain diseases. We do find manifestly heterozygous women affected whose fathers are healthy, which according to the rule of sex-linked recessive hereditary diseases is impossible. A possible explanation is to admit that the recessive gene may become dominant in the carriers.

This change in dominance is principally found in the families subject to hereditary atrophy of the optic nerve (Leber's disease). We are familiar with a number of pedigrees in which part of the carriers are also affected with atrophy of the optic nerve (cf. the work of Julia Bell). This change in dominance is particularly frequent in the cases observed in Japan (Kawakami).

According to Kawakami, the occurrence of change in dominance varies for the different countries :—

Germany	3.5 %
France	11.9 %
England	19.8 %
Japan	30 %

This change in dominance has been observed in other sex-linked recessive diseases (Nystagmus, Hemophilia, Pelizeus-Merzbacher's disease), and exceptionally in colour-blindness. By the change in dominance, several generations in succession may be affected so that one might be led to think that the disease was transmitted by the dominant mode. The principal difference, however, between the sex-linked recessive mode of transmission with change of dominance and true dominance is that the disease cannot be transmitted from father to son if the defect is a sex-linked recessive one.

The explanation suggested by Punnet (1933) that sex-linked recessive defects may also follow the dominant mode of transmission if one supposes that a dominant factor in an autosome inhibits the dominance of the carrier's normal gene in the x-chromosome seems inadmissible to me. Punnet's theory is incompatible with the laws of dominance. In dominance, the defect is frequently transmitted from father to son, which would be impossible according to Punnet's hypothesis. The same objection holds for Hogben's hypothesis (1932) which supposes the dominance of two genes for the Japanese cases of Leber's disease.

Given the fact that the carriers may occasionally be affected, the problem is to know if the dominance of the normal gene is an absolute one in heterozygotes. The horticulturists claim often to distinguish homozygous from heterozygous plants even in cases of so-called absolute recessivity. In man, Wieland (1933) and Ingeborg Schmidt (1934) have recently been able to show that the carriers of colour-blindness often presented slight modifications of colour vision, which could not be discovered by the habitual methods. It seems indicated therefore, to examine other heterozygotes to determine if it is possible to discover, at least for certain defects, local abortive modifications or constitutional variations related to the recessive gene. I have observed for example, that buphthalmia occurs in small gracile subjects, and that, very often, the heterozygous parents are of a similar type. These observations are still too rare to permit definite conclusions to be drawn, but it is obvious that it would be of primordial importance to be able to recognize the heterozygous individuals with more or less certainty.

2, *Lossen's Law.*

According to Lossen, hemophilia is only transmitted by the carriers, and the children of the diseased individual are untouched. This law applies equally to Leber's disease.

Schloessmann has been able to show, however, that hemophilia may exceptionally be transmitted by the men, and that it is probable that there are also exceptions for hereditary optic neuritis. The examples cited in the literature as proof of these exceptions seem unconvincing to me, for they are generally based upon the unverified assertions of the patient. It is true that Lossen's law seems to be supported by the fact that the mortality of the diseased men is relatively high, as they rarely marry ; that their

daughters generally have few children ; and that their grandsons have not yet reached the critical age at the time the observation is published.

According to the modern statistics, it may be affirmed that the men suffering from Leber's disease do not generally transmit the disease to their children.

3. *Among the sisters of the diseased there are too many carriers, and among the brothers too many diseased.*

Meyer-Riemsloh, Vogt and Waardenburg have drawn attention to the fact that most of the sisters of the patients with Leber's disease are carriers. According to the theory, there should be 50 % of carriers. In studying 20 published pedigrees in which the sons had passed the critical age, I found the ratio between carriers and normal sisters to be 90 : 14.02 or 6.4 : 1, whereas according to the formula this ratio should equal unity. In reality this ratio should be still further modified in favour of the carriers in view of the fact that the latter, due to their small number of progeny, do not always have affected sons.

The number of sons affected is also too great. Julia Bell has found a ratio of 2.3 to 1 between the diseased and normal among the sons of the carriers. This figure is also discordant with the theoretical proportion of 1 to 1. One might object that families with several affected members are more likely to have their pedigrees published than those with one or two. On the other hand, there are very often sons in these families who have not attained the critical age at the time of publication, who may increase the number of diseased members. It is therefore very probable that there is a real exaggeration of the number of men affected. We cannot discuss the different theories which have been suggested to explain these facts. (See the papers of Franceschetti, Waardenburg, etc.)

V. *Digeneticism*

It has long been supposed that certain hereditary diseases in man were due to the modification of two or more genes (polygeneticism).

Two dominant genes are in play if a family disease generally appears in a single generation without consanguinity.

The determination of digeneticism and above all of polygeneticism in man is always very difficult because of the small number of offspring in the human race. If two dominant genes are involved, one-fourth of the children are affected, if one of the parents is heterozygous for one of these genes, and the other for the second. The proportion of diseased to sound children is therefore 1 to 3, and corresponds to that of recessive defects. If one of these diseased individuals marries, one-fourth of his children are again diseased, while for recessive defects, the children are generally untouched. The appearance of the disease in several consecutive generations is therefore possible but improbable, inasmuch as only one-fourth of the children are affected as we have already seen.

Several years ago, I suggested that keratoconus was due to two dominant genes. Recently Hogben (1932) has been able to show that glioma of the retina was also probably due to two dominant genes. This may perhaps explain the fact that individuals suffering from glioma of the retina sometimes have diseased children, despite the fact that the marriage is rarely consanguineous. Penrose (1932) believes that digeneticism should also be incriminated in Mongolian idiocy.

I am convinced that it will be possible, sooner or later, to show for a number of defects whose mode of transmission now seems obscure (cranial anomalies, etc.) that polygeneticism is involved.

It has been suggested for some diseases, that in addition to the modified gene, there were others which inhibited or stimulated its action. This theory is equivalent to that of digeneticism.

VI. *Sex-linked dominance*

Nystagmus is often transmitted as a sex-linked recessive defect, but it is also transmitted, and occasionally in the same family, by irregular dominance. It is for this reason that Lenz has suggested that it was transmitted not by simple dominance, but rather by sex-linked dominance.

According to the formulae, were this true, we should find twice as many women as men affected, which is not the case. For Lenz, this is explained by the fact that the dominant sex-linked gene manifests itself in only 30 to 50 % of the heterozygous women, or in other words, that the penetration of the sex-linked gene is from 30 to 50 %

in the female. In my opinion, there is in practice no difference between sex-linked dominance with 50 % of penetration and the sex-linked recessive mode with change in dominance in 50 %. There is, however, a distinct difference between simple and sex-linked dominance. In the latter, as opposed to the former, the disease can never be transmitted from father to son.

VII. *Homochronous and homologous manifestations of hereditary diseases*

The tendency to confuse congenital and hereditary diseases is all too frequent even to-day. There are nevertheless a number of defects which only become manifest after birth. In the members of one family, and especially of the same generation, these diseases appear at nearly the same age (homochronous manifestation).

The ocular defects which appear late are, especially, late ptosis, keratoconus, cataract, tapeto-retinal degeneration (macular defects, etc.), juvenile amaurotic family idiocy, glaucoma, and a number of senile diseases.

Some diseases, although congenital, appear only long after birth, either because the symptoms pass unobserved (night-blindness), or because they are progressive (retinitis pigmentosa, myopia). The malformations are ordinarily manifest at birth, the abiotrophies generally appear after birth.

We speak of a homologous manifestation when a hereditary disease appears in the same generation in the different branches of the same family. Homologous manifestation is especially observed in diseases of nervous origin. In ophthalmology, this is principally the case for cataract in dystrophia myotonica, and certain tapeto-retinal degenerations (family diseases of the macula).

VIII. *Anticipation*

By anticipation, we mean the precocious manifestation of a hereditary disease in the following generation. In general, anticipation accompanies a more serious diseased state (glaucoma, cataract in dystrophia myotonica, etc, etc.). Certain ordinarily senile diseases, are often hereditary and familial when they appear precociously. Glaucoma and cataract are, for example, distinctly hereditary in the congenital or juvenile forms. The presenile and senile forms are

less often familial. It may evidently be objected that the critical age is often not reached, thereby preventing the familial appearance of the disease.

Many authors do not accept the doctrine of anticipation. Lenz maintains that cases of precocious appearance of a disease are more likely to be published than the late cases, and that in this fashion the anticipation is merely illusory. This does not explain the fact that precocious manifestations are often lacking in the previous generations and that there is no reason why they should not be mentioned. I share the opinion of Usher (1933) who admits the existence of anticipation.

In conclusion, we may say that the principal difficulties and exceptions arising in the application of the Mendelian formulae to man are the following :—

1. Irregular dominance.
2. Different modes of transmission for defects with the same clinical picture.
3. Late manifestation.

Table 4 indicates the probability for the offspring to be affected in the different modes of transmission.

TABLE 4

MODE OF TRANSMISSION AND PROBABILITY THAT OFFSPRING WILL BE AFFECTED

1. Regular dominance.	50 % of the children affected ; children of sound individuals never affected (foresee late manifestation).
2. Irregular dominance.	Some of the children affected (occurrence depends upon the penetration of the pathological gene ; children of apparently healthy parents may be affected).
3. Sex-linked recessivity.	General formulae (see Table p. 32).
4. Simple recessivity (consanguinity frequent).	Two-thirds of the brothers and sisters, and 100 % of the children are carriers. Rarely manifested in the descendants if the disease is infrequent.
5. Digeneticism, two dominant genes (consanguinity infrequent).	One-fourth of the children affected.

C. — Single cases of hereditary diseases

For the majority of hereditary diseases of the eye, the mode of transmission has been determined by the study of the family trees. The single cases of diseases ordinarily hereditary have been neglected by the investigators. The appearance of single cases may result from several causes.

1. *Single cases of recessive diseases*

Single cases of recessive diseases should be quite frequent, for when the parents are heterozygous, one-fourth of the children are affected and because human beings have a small number of offspring.

The proportion of family cases to single cases can be readily calculated. The proportion of diseased to sound children is 1 : 3. The probability that in n children there be none, one, or several diseased is expressed by the factors obtained in developing the binomial $(1 + 3)^n$. The first factor expresses the probability of all the children, the second of n-1 children, etc., the next to the last of one child, and the last of none of the children being diseased.

In developing, for example, the binomial $(1 + 3)^4$, we obtain for four children the following probabilities :—

4 children diseased	1	family cases. . . .	67 (26.3 %)
3 children diseased	12		
2 children diseased	54		
1 child diseased.	108	isolated cases . . .	108 (42.1 %)
no children.	81	no cases.	81 (31.6 %)
Total.	256		

Thus, for 256 heterozygous marriages, several children are diseased in 26.3 % of the cases, only one child in 42.1 % and in 31.6 % no children are diseased.

The following table shows the proportion between family and single cases according to the number of children.

TABLE 5

PROPORTION BETWEEN FAMILY AND SINGLE CASES OF RECESSIVE HEREDITARY DISEASES ACCORDING TO THE NUMBER OF CHILDREN

Number of Children	Number of Cases		Percentage of Cases	
	Family	Single	Family	Single
1	0	1	0	100
2	1	6	14.5	85.7
3	10	27	26	73
4	67	108	38.3	61.7
5	376	405	49.4	50.6

This table shows that in families with 5 children, 50 % may have one child diseased, and 50 % several.

Family cases are more interesting than solitary cases for the investigators, and in consequence, the latter are less frequent in the literature.

Nettleship (1907) found 250 single cases (25.6 %) and 976 family cases among 1,226 published pedigrees of retinitis pigmentosa. In his personal records, the isolated cases attained 41.1 %. Usher in his practice has observed 52.5 % of solitary cases of retinititis pigmentosa.

2. *Single cases of dominant diseases*

It is obvious that every dominant disease must appear in the genealogical tree as a solitary case.

Let us see how a hereditary disease may first appear.

a. *Mutation*

According to Bauer, mutations or spontaneous idiovariations are as frequent in man as in animals. He believes that mutations are primarily responsible for malformations.

b. *Change of dominance and manifestation of latent genotypic alterations*

The spontaneous appearance of a dominant disease may be due to a gene, recessive for generations, becoming dominant. It is probable, that other genes, of the same or other chromosomes, influence the appearance of the disease.

This is all the more probable, because as we have already seen, the normal characters, and also the pathological conditions, are due to a number of genes. To my mind, the manifestation of latent genotypic defects, is more frequent than is generally believed, while too much importance is attached to mutation.

The homologous appearance of an anomaly in different branches oft he same family is the principal evidence in favour of the manifestation of latent genotypic defects. I may mention, in support of this theory, the famous pedigree of Friedreich's hereditary spinal ataxia observed in Switzerland, and published by K. Frey (1912). In the descendants of a personage of the sixteenth century, 15 cases of the disease were observed in 4 branches in the eleventh generation, and in 2 branches in the twelfth generation. The disease had not been observed in the ancestors. It is obvious that the appearance of these 15 cases cannot be explained by mutation. It is more likely that they were the manifestation of an until then latent genotypic defect, in which the repeated consanguinities of the ancestry probably played a part. To explain the homologous appearance of the disease in this pedigree, I draw attention to the analogy between homologous manifestation and anticipation. We have already seen that anticipation is the precocious and aggravated manifestation of a defective gene in the succeeding generation. One may suppose that homologous manifestation is the first phenotypic appearance of a gene, whose importance has increased from generation to generation. I have had occasion to examine the descendants of two branches of the ataxic family in question, and have observed a macular degeneration in 4 members of the following generations. This shows that in the families presenting phenomena of cerebro-spinal degeneration, tapeto-retinal defects may appear as equivalents.

Klainguti has also found a family disease of the macula in several members of different branches of one family. We have already cited other examples of homologous appearance of ocular diseases (family corneal degeneration, cataract in dystrophia myotonica).

c. *The influence of exogenous factors* (*peristasis*)

Too great an importance has long been accorded to exogenous factors in the etiology of modifications of the idioplasm. On the authority of Ida Mann, nearly all the experiments seeking to produce heritable modifications of the idioplasm in animals have been complete failures.

3. *Pseudo-sporadicity in polyphenia*

The hereditary eye diseases are often associated with modifications of other organs, especially of the brain. Deaf-mutism in retinitis pigmentosa, ectopia lentis in Marfan's disease and amaurotic family idiocy may be recalled as examples. A whole series of affections of the retina and optic nerve, as well as the anomalies of refraction and strabismus which are accompanied by affections of the brain, also belong to this class. These manifestations are examples of polyphenia. In other words, they are syndromes resulting from a single gene or group of genes (1).

In polyphenia, one often finds members of the diseased family with one or the other of the two equivalent defects. I am of the opinion of Usher (1933), who considers that sporadic cases of hereditary diseases would be less frequent if greater importance were attached to the general examination of the other members of the family, who often present diseases of other organs, which may be considered equivalent to the ocular defect.

4. *Sporadic exogenous cases mistaken for hereditary diseases*

The exogenous diseases very often present some analogy with the hereditary diseases. Thus, for example, toxic retrobulbar neuritis may present the same symptoms as Leber's disease. Many authors too, confound hereditary and secondary buphthalmia. The difficulties are particularly great for the tapeto-retinal degenerations (retinitis pigmentosa, family disease of the macula, etc.), whose clinical picture may have many resemblances to those of inflammatory diseases, especially syphilis.

The differential diagnosis is also very difficult for juvenile atrophy of the optic nerve. It may be extremely hard to decide whether the disease is of hereditary origin, secondary to cerebral disease (tumours, meningitis, hydrocephaly), or syphilitic.

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(1) The opinion is often advanced that polyphenia is due to the joining of two genes. The diagnosis of joining of two genes must be distrusted. If two different anomalies are generally related, a union of genes becomes unlikely. In an individual in whom one of the two genes, whose union is supposed, is defective, there is joining of this gene with a normal gene. As crossing-over does not ordinarily separate two contiguous genes, it is very unlikely that the two defective genes be united in one chromosome. A negative correlation of the two diseases in question results in the population, if there really is coupling of two genes.

All these difficulties emphasise the necessity for studying not only the family cases, but above all the sporadic cases, and especially the members of their families, in the bounds of possibility, as requested by Usher and Julia Bell. The study of the isolated cases will probably permit to distinguish better the sporadic hereditary diseases from those which are not. The statistics we possess to-day are incomplete for a number of points which it would be interesting to study. They are,

1. The frequency of isolated cases in proportion to family cases,

2. The proportion between presumably hereditary isolated cases and family cases,

3. The occurrence of hereditary diseases in the population.

II. — THE INCIDENCE OF HEREDITARY AND ACQUIRED BLINDNESS

To consider measures against hereditary blindness, it is indispensable to know exactly, the number of cases of the anomalies whose mode of transmission has been exposed in the preceding chapter. The available statistics are very vague on this subject. These statistics are of only relative value, principally for the following reasons :—

1. They are concerned with a selected material based upon the number of patients institutionalized in homes for the blind, or seen by a physician in his practice.

2. The official statistics on blindness ordinarily make no distinction between hereditary and acquired blindness, or they are based solely upon the assertions of the patients.

3. The evaluation of the number of hereditary affections is often based upon the frequency of congenital anomalies. There is much evidence that not all hereditary diseases are congenital. The result is that the figures given for the hereditary diseases are generally too low.

4. The statistics based upon the observations of an oculist in his practice are more valuable without, however, being more exact. This is due to the fact, that the differential diagnosis of hereditary from acquired disease is very often difficult to make without a general examination of the

patient (Wassermann reaction, etc.), and of the other members of his family. This difficulty is of the greatest importance for tapeto-retinal diseases, atrophy of the optic nerve, and diseases of intra-uterine, and therefore exogenous, origin.

Nevertheless, despite these difficulties, it should be possible to establish much more accurate statistics than we now possess.

A. — Definition of blindness

We are not concerned here with the theoretical definition of blindness, or abolition of the perception of light, but with the definition of what may he called practical blindness. We must not confuse complete blindness with low vision which prevents the patient from following a trade for which sight is indispensable. Ordinarily, an individual, who cannot count the fingers against a black background at a distance greater than one metre, is considered blind. This corresponds to a maximum vision of 1.5/60. In Germany, an individual who, even with spectacles, cannot orient himself in an unfamiliar place is considered blind. This definition approximately corresponds to the classical definition of Axenfeld, which says. "Is blind, he who cannot earn his living with the aid of his eyes."

These definitions have the advantage from the practical point of view, of providing for cases of narrowing of the visual field. According to Waardenburg, in Holland, the definitions of blindness vary slightly according to the age of the individual.

Individuals under 14 years of age are considered completely blind with vision inferior to 5/60, and incompletely blind with vision from 5/60 to 1/6. Over 14 years of age, vision inferior to 1.5/60 is considered as complete blindness, and from 1.5/60 to 1/10 as incomplete blindness.

The limit for blindness in children is higher. This classification has certain advantages, but from the statistical point of view, it is less exact, for a patient may pass from one group to the other at 14 years, without any change in the acuity of his vision.

What Waardenburg calls incomplete blindness, approximately corresponds to what the other authors call amblyopia [see table 6].

TABLE 6

DIAGRAM SUMMARIZING THE DIFFERENT DEFINITIONS OF COMPLETE AND INCOMPLETE BLINDNESS AND AMBLYOPIA

<table>
<tr><th rowspan="2">Author</th><th rowspan="2">Amaurosis</th><th colspan="5">Vision</th></tr>
<tr><th>$>$ 1/60 (1.5/60)</th><th>1/60 (1.5/60-1/25) (5/60)</th><th>5/60-1/10</th><th>1/10-1/6</th><th>1/6-1/3</th></tr>
<tr><td>Axenfeld</td><td colspan="3">Unable to earn living with aid of sight</td><td colspan="3" rowspan="2">Amblyopics</td></tr>
<tr><td>Zade</td><td>Theoretical blindness</td><td>Practical blindness</td><td>Social blindness</td></tr>
<tr><td>Waardenburg children $<$ 14</td><td colspan="3">Complete blindness</td><td colspan="2">Incomplete blindness</td><td></td></tr>
<tr><td>adults $>$ 14</td><td colspan="2">Complete blindness</td><td colspan="2">Incomplete blindness</td><td colspan="2"></td></tr>
</table>

It is obvious that the statistics of hereditary diseases should include not only complete blindness, but incomplete blindness and amblyopia. This is all the more important, because a large proportion of the patients suffering from hereditary diseases are only partly blind. This is principally true of the myopics, who are often classed among the amblyopics.

The superior limit for admission to the special classes for amblyopia varies in different countries, as is shown by the following table.

TABLE 7

SUPERIOR LIMITS OF VISUAL ACUITY FOR ADMISSION TO THE SPECIAL CLASSES FOR AMBLYOPIA

Country	Vision	Authors
France	0.2 -0.3	Redslob, Villey.
Switzerland	0.2 -0.5 (1)	Dufour.
Poland	0.25-0.3	Szymanowsky.
Denmark	0.25	Holm.

(1) Limit for myopics.

To summarize, we may say that the conception of total and partial blindness varies slightly from one country to another. An international agreement on this point should, however, considerably simplify the task of the statisticians.

B. — General incidence of blindness

The following statistics presented to the International Congress of Ophthalmology in Amsterdam in 1929, show that the number of blind varies considerably from one country to another.

The statistics reproduced below concern 36 nations, with a total population of 950 million. The average number of blind is 13.3. It is relatively high. The average is raised principally, by those countries in which blindness results from infectious diseases (trachoma, small-pox, ophthalmia neonatorum). In Europe and North America, the number of blind varies between 4 and 12 (per 10 000). The differences observed are due to the varying frequency of infectious diseases and to the manner in which the statistics are collected.

TABLE 8

Number of Blind per 10,000 *population*

Palestine	166.7	United States	8.2
Egypt	119.7	France	8.1
Persia	24.9	Europeanised South Africa	7.6
Latvia	22,5	Argentine	7.5
Esthonia	21.7	Finland	7.1
Europeanised North Africa	20,7	Italy	6.9
Algeria	18.8	Czechoslovakia	6.8
Japan	17.0	Poland	6·7
Russia	16.9	Sweden	6·1
Lithuania	15.4	Switzerland	5·7
British India	15.0	Germany	5·3
Dutch East Indies	14.9	Roumania	5·1
Portugal	12.0	Denmark	4·5
Great Britain	11.45	New Zealand	4·3
Mexico	11.3	Holland	4·3
Spain	11.1	Greece	4·1
Hungary	10.5	Canada	3·9
Norway	10.1	Belgium	3·7
Bulgaria	10.0		

Has the number of blind increased in recent years?

Bickerton (1934) has published a sensational paper on

this question. He gives the following figures for the number of blind in England (1).

TABLE 9

Year	England and Wales	Scotland	Total
1919 . . .	25,840		
1929 . . .	52,727		
1930 . . .	56,853	8,516	65,369
1932 . . .	62,488	10,000 (?)	72,727 (of whom 2,000 war blind)

Bickerton arrives at the following conclusions. In the last 12 years, the number of blind has increased by 35,000 ; from 1929 to 1930, the increase was 4,126, or 11 a day. He believes that the total number of blind in Great Britain is 250,000 for it must be recalled that the well to do, children under 6 years of age, and the blind unaware of their right to a pension, are not included in the official statistics. Do the figures put forward by Bickerton really prove an increase in the number of blind ? I share the opinion of Fleischer and Waardenburg, who believe that this increase is fictitious, and is explainable by the fact that an old age pension is given to the blind after 50 years of age. They therefore have every incentive to declare themselves. This explanation is all the more probable as the number of blind is decreasing in other countries. The medical, prophylactic, and social steps taken in England, are in no way inferior to those in force in other countries. There is no reason, therefore, why this country should be an exception.

The following table compares the statistics presented at the Amsterdam Congress with the earlier ones.

(1) The total population is unfortunately not indicated.

TABLE 10

Country	Amsterdam Congress Statistics (1929)	Deutsch	Cohn (1886)
British India. . . .	14.9 —	16.1 (1906)	
Portugal	12.0 —	13.4 (1903)	21.9
Great Britain . . .	11.45 +	7.9 (1901)	8.8
Hungary	10.5 +	10.0 (1901)	12.8
Norway	10.1 +	8.46 (1900)	13.6
United States . . .	8.2 —	8.5 (1900)	9.7
France	8.1 +	7.0 (1901)	8.4
Italy	6.9 —	11.8 (1901) +	7.5
Sweden	6.1 —	6.64 (1900)	8.0
Switzerland.	5.7 —	7.2 (1900)	7.6
Holland	5.5 +	4.6 (1909)(*)	(1889) (*) 4.7
Germany	5.3 —	6.1 (1900)	8.5
Belgium..	3.7 —	4.4 (1900)	8,1

+ increased.
— decreased.
* Waardenburg.

The table shows that the number of blind has clearly diminished in all the countries (except Italy) from 1868 to 1900. This amelioration is certainly due to the medical and hygienic measures applied. From 1900, the decrease is much less clear. Italy, Holland, Norway, the United States, and France even indicate a slight increase (0.5-1.5). This increase is greatest in Great Britain (3.55) (1).

It is obvious that in those countries in which the infectious diseases of the eye were vigorously attacked early, the decrease is now less clear. The increase in certain countries is, as we have just said, also due to an improvement in the statistical technic. What is more, Waardenburg has drawn attention to the fact that the longevity has been increased in recent years, and as half of the blind are over 60, the repercussion on the statistics is quite considerable. In Holland, Waardenburg has found blindness twice as frequent in the aged as in the young.

In general, the frequence of blindness is the same in both sexes.

In Holland in 1920, the ratio between men and women blind was 5.6 to 5.4, or 1.03 : 1.

In Germany, the statistics on blindness for 1925-26 gave

(1) The wide prevalence of ophthalmia neonatorum seems to play a part (Bickerton).

men 57.7 %, women 42.3 % (total 33,192) which corresponds to the proportion of 1.36 : 1 (1).

An excess of blind men may be explained by the fact that men are more exposed to exogenous influences (traumatisms, syphilis, intoxications).

This excess of male blind chiefly affects the young individuals. Here are the figures cited by Waardenburg for the frequency of blindness in children of both sexes.

TABLE 11

Age	Boys	Girls	Difference
0-3 years	1.6	1.2	0.4
3-16 years	2.6	1.9	0.7
Total	2.3	1.7	0.6

The ratio between boys and girls is 1.35 : 1.

The excess of blind boys may be due to the fact, that certain hereditary anomalies, and especially the sex-linked recessive diseases, as we shall see later, are more frequent in the male sex.

To summarize, our knowledge of the occurrence of blindness enables us to say that on the whole, blindness has diminished, and that the increase observed in certain countries is probably due to an improvement in the statistical technic. As long as we have no statistics based upon a detailed examination of the patient by an oculist, all conclusions that may be drawn from them will only have a relative value (2).

C. — The age at which blindness is manifested

The statistics indicating the age at which blindness appears, are also very often inexact, and have the ordinary faults which have already been mentioned (selected material, information given by the patient). In addition, they do not

(1) Feilchenfeld.

(2) According to Bickerton, the certificate of blindness introduced in England is also only of relative value, the more so because it is given to patients desirous of obtaining a pension. The important statistic gathered in Germany in 1925-26 only includes 15 % of the blind examined by an oculist.

distinguish between hereditary and acquired diseases. We shall however, give two statistics concerning the age at which blindness appeared.

TABLE 12

AGE AT WHICH BLINDNESS APPEARED IN 1449 CASES (Fleischer)

	0-20 YEARS	20-40 YEARS	> 40 YEARS	UNKNOWN
Men	67.3 %	15.3 %	15.8 %	1.6 %
Women	68.8 %	11.8 %	18.5 %	0.9 %

This table shows that between 20 and 40 years, more men are affected, while more women are affected after 40 years.

TABLE 13

APPEARANCE OF BLINDNESS IN 2,133 CHILDREN (Hirsch)

CONGENITAL	0-1 YEAR	1-5 YEARS	6-10 YEARS	11-15 YEARS
31 %	23.1 %	25.4 %	13.4 %	7.1 %

D. — INCIDENCE OF HEREDITARY BLINDNESS

As the statistics on blindness are generally not very exact, it is not astonishing that those on congenital blindness be even less exact. If conclusions are to be drawn from them, it must be borne in mind, that they can only be rough approximations.

The statistics ordinarily distinguish between congenital and acquired blindness.

The occurrence of congenital blindness may be roughly estimated from the statistics of homes and schools for the blind, which are often made by oculists.

For acquired blindness, it is practically impossible to rely upon the statistics to separate the cases which are hereditary, and those which are not. This is not only due to the imperfections of the statistics, but also to the fact, that it becomes increasingly difficult to distinguish the hereditary cases from the others, as the age at which the blindness appears advances.

Congenital cataract, for example, is principally hereditary, except the complicated cataracts, which are generally of exogenous origin. The latter are easily distinguished. It is difficult to determine the part of heredity in senile and presenile cataract. If senile manifestations are considered the consequence of genotypic influence, all senile cataracts must be classed as hereditary. It would then be necessary to include in this class, senile glaucoma, diseases of vascular and diabetic origin, etc. The application of this theory would present enormous difficulties. It may be claimed that eugenics is of little importance in senile cataract, but this disease is of interest in heredity, because of anticipation. Indeed, the descendants of patients suffering from senile cataract are occasionally affected with presenile, juvenile, and even congenital cataract. The same holds true for a number of ordinarily senile diseases, which may appear precociously among the descendants (glaucoma, diseases of the macula, etc.).

Let us now look at the statistics for congenital blindness. The greater number are, as we have seen, based upon the examination of blind children. The figures given for congenital blindness are, therefore, much too large. The following table summarizes the statistics which make more or less allowance for this error.

TABLE 14

Country	Year	Percentage of congenital blindness	Author
Germany	1925-26	14.4	Official Statistics for 1925-26.
Holland		14.1	Waardenburg.
Norway.	1920	13.4	Quoted by Fleischer
Bulgaria	1926	13.8	Quoted by Fleischer
Ukraine	1926	16.9	Quoted by Fleischer
Westphalia	1922	17.1	Westphalian Society for the Welfare of the Blind.
Wurtemberg	1894	16.4	Krailsheimer.
France	1920	18.4	Danrrieux.

This table indicates that recent statistics for congenital blindness give a frequency of approximately 15 %. If we examine the table based on the statistics of homes for the blind, the frequency appears to be much higher.

TABLE 15

FREQUENCY OF CONGENITAL BLINDNESS AMONG THE INMATES OF HOMES AND CLASSES FOR THE BLIND

Author	Year	Cases	Percentage of congenital blindness
Huebner	1924	2,757	26
Norrie	1927	578	33
Hirsch.	1902	2,210	30
American Committee on Statistics of the Blind	1933-34	2,653	40
Waardenburg		114	50

According to this table, the frequency varies between 26 and 50%. These differences are due, for one thing, to the fact that this table deals with selected material, and for another, to the fact that the conception of congenital blindness varies with the authors. Some of them, like Waardenburg, include those cases in which blindness appears shortly after birth.

What part is played by hereditary diseases in congenital blindness?

To answer this question, only the statistics based upon an ophthalmological examination of the patients may be used. The following table gives the results obtained by Waardenburg, which he has been kind enough to place at my disposal.

TABLE 16

Probable frequency of hereditary congenital blindness (114 cases) (Waardenburg)

Eye disease	Frequency in %	Frequency of cases of probable hereditary origin
Congenital malformations . . .	28	28
Congenital atrophy of the optic nerve	24.6	11
Atrophy of the optic nerve in brain diseases	6.1	approximately
High myopia and detachment of the retina.	3.5	3.5
Bilateral glioma	0.9	0.9
Diseases of the iris and sympathetic ophthalmia	15.8	—
Leucoma (gonorrhea, etc.) . .	14	—
Atrophies of the globe (gonorrhea, etc.)	4	—
Miscellaneous (Optic nerve, retina, uveal tract, diseases of the sinuses).	2.7	—
Total	100	43.4

For comparison, here are the results obtained by the American Committee on Statistics of the Blind. This investigation made in 1933-34 is based upon the ophthalmological examination of 2,653 children enrolled in certain schools and classes for the blind in the United States. (This figure represents 50 % of the pupils in these schools.) I have arbitrarily added columns 2 and 4 to this table. In comparing columns 3 and 4, it will be noticed that of 40 % of congenital diseases, 24 %, more than half, are hereditary. At first sight, this figure may seem rather high, but it must be recalled, that in column 3, we are dealing with strictly congenital diseases. The figure of 40 % given in the statistics seems low to me. The frequency of albinism is given as 2.3 % of which only 0.8 % is considered congenital. I find it difficult to imagine albinism not being congenital. If columns 1 and 2 are compared, it may be estimated that 43 % of the cases are hereditary. The figure corresponds exactly to that of Waardenburg, if consideration is taken of the fact that the investigation of the latter is not confined to strictly congenital cases. The number of hereditary cases is certainly even greater for incomplete than for complete blindness.

Among the pupils of schools for the partially blind, this

TABLE 17

Congenital and hereditary blindness among 2,653 children enrolled in certain schools and classes for the blind in the United States (Lewis)

Cause	Frequency 1.	Probably hereditary 2.	Congenital or prenatal 3.	Probably congenital and hereditary 4.	Reported hereditary by oculist (congenital or familial) 5.
Albinism	2.3	2.3	0.8	0.8	1.5
Aniridia	0.9	0.9	0.8	0.8	0.2
Anophthalmia	0.3	0.2	0.3	0.3	0.1
Megalophthalmia (infant. glaucoma)	2.9	2.7	2.7	2.7	0.1
Developmental and degenerative changes of the eyeball	2.7	2.0	2.2	1.8	0.4
Dislocated lens	1.4	1.4	0.8	0.8	0.6
-Lens opacity (cataract)	16	14.0	12.9	10.0	2.9
All diseases of cornea	14.6	0.2	0.1	—	—
Retinal degeneration	3.0	2.0	1.3	0.6	1.1
Choroiditis, retinitis, chorio-retinitis	7.4	2.0	1.4	0.2	0.7
Other diseases of choroid and retina	4.2	1.0	0.2	0.1	0.05
All diseases of iris and ciliary body	2.3	—	—	—	0.05
Optic nerve atrophy	14.4	7.2	4.9	2.0	1.7
Other diseases of the optic nerve	2.7	0.5	0.3	—	0.2
All diseases of the vitreous humour	0.2	—	0.05	—	—
Myopia	3.5	3.5	2.3	2.3	1.1
Other refraction errors	1.9	1.9	1.7	1.7	0.2
Miscellaneous and ill-defined	2.5	1.5	0.6	0.1	0.4
Total	100. %	43.1 %	40 %	24.2 %	11.8 %

frequency evidently varies with the conditions for admission to these schools in the different countries. In consequence, the percentage of school children in these special schools varies greatly as is shown by the following table.

TABLE 18

PERCENTAGE OF SCHOOL CHILDREN IN SCHOOLS FOR THE PARTIALLY BLIND

Hamburg	0.06 %
Strassburg	0.1 %
Dortmund	0.1 %
Berlin	0.2 %
United States	0.1-0.2 %
Zurich	0.25 %
London	1 % (1) (0.13 % in 1923)

According to this table, one may conclude that 0.1 to 0.2 % of the total number of school children are in need of schools for the partially blind.

The following table shows the relation between probably hereditary diseases and others among the pupils of classes for the partially blind in Zurich.

These statistics demonstrate that 88.5 % of the cases are probably hereditary. This is principally due to the fact that the general hygiene, and the social and medical measures taken in Zurich leave nothing to be desired. There is not a single case resulting from ophthalmia neonatorum (which is not only due to the prophylaxis, but also to the parenteral treatment with milk). In addition, the part played by syphilis is of less and less importance in Switzerland.

We may say therefore, that the great majority of cases of blindness in children, ophthalmia neonatorum and syphilis apart, are hereditary (2).

(1) There is a relatively large proportion of myopics in the London schools for the partially blind.

(2) In 37 cases of amblyopia in children, Waardenburg, found 58 % of hereditary origin.

TABLE 19

DISTRIBUTION OF EYE DISEASES AMONG 61 PUPILS ENROLLED IN CLASSES FOR THE PARTIALLY BLIND IN ZURICH (1925-1934) (1)

EYE DISEASES	BOYS	GIRLS	TOTAL
I. *Probably hereditary :*			
Aniridia	1.65	—	1.65
Ectopia lentis	1.65	—	1.65
Congenital cataract	6.5	4.9	11.45
Microphacia	—	3.3	3.3
Microphthalmia	—	1.65	1.65
Albinism	1.65	—	1.65
Aplasia of the macula with nystagmus	4.9	3.3	8.2
Diseases of the macula. . . .	1.65	1.65	3.3
Keratoconus	3.3	—	3.3
Nystagmus with amblyopia. .	6.5	3.3	9.8
High myopia	13.1	18.0	31.1
Hypermetropic astigmatism with amblyopia	4.9	4.9	9.8
Myopic astigmatism with amblyopia.	—	1.65	1.65
Total.	45.8 %	42.7 %	88.5 %
II. *Not hereditary :*			
Leucoma, scrofulous keratitis .	1.65	4.9	6.65
Interstitial keratitis	1.65	—	1.65
Chorio-retinitis (congenital syphilis)	—	1.65	1.65
Irido-cyclitis	—	1.65	1.65
Total	3.3 %	8.2 %	11.5 %

There are no statistics which can give us exact figures on the frequency of hereditary blindness in the total number of blind, for the reasons we have already mentioned. I am convinced, however, that the estimate of 8 % by Howe, which is accepted by Fleischer, is much too low. I agree with Waardenburg and von Verschuer, who consider 33 % of the cases of blindness to be hereditary.

We may conclude approximately, and more or less arbitrarily, as follows :—

1. 15 % of the blind are so at birth.
2. 50 % of blind children are so congenitally. The percentage is even higher for amblyopia.
3. 50-60 % of congenital blindness is hereditary.

(1) I owe these unpublished statistics to my mother, Dr. B. Franceschetti-Spitzer, oculist of the Zurich schools, who has been kind enough to place them at my disposal, for which I thank her.

4. 40 % of juvenile blindness is hereditary. Here too, the percentage is higher for amblyopia.
5. 33 % of blindness is hereditary.

It is obvious, that these estimates are only valid for those countries in which trachoma, small-pox, and ophthalmia neonatorum rarely cause blindness. For the other countries, allowance must be made for the infectious cases.

E. — The incidence of the different hereditary eye diseases

The statistics enable us to determine quite accurately the incidence of congenital and infantile hereditary diseases. We have no information whatever about the incidence of hereditary diseases manifested after 20 years of age, like Leber's disease, glaucoma, cataract, etc. Information concerning certain precociously manifested hereditary diseases will be found in the following table. Too much importance must not be attached to the figures quoted, for the calculations of the different authors are not comparable. P. Lewis, Hart, and Norrie include congenital blindness ; Lamb counts only certainly hereditary cases ; and Waardenburg includes cases manifested late (Leber's disease, etc.).

TABLE 20

Incidence of different infantile and congenital hereditary diseases (1)

Eye diseases	Waardenburg	Lewis	Hart	Norrie	Lamb	Hirsch
Buphthalmia . . .	26.7 %	6.7 %	22 %	12 %	20 %	9 %
Retinitis pigmentosa.	19.5 %			12 %	6 %	16 %
Microphthalmia / Anophthalmia / Coloboma	17.9 %		15 %	14 %	19 %	18 %
Congenital cataract	17.9 %	32.2 %	33 %	22 %	36 %	35 %
Hereditary optic atrophy	7.3 %	(12.2 cong.)				17 %
Albinism	5.3 %	2.0 %				1 %
Aniridia	2.9 %	2.0 %			2.0 %	
Total colour-blindness	2.5 %					

(1) Where the figures are not given, the authors do not indicate the occurrence of the disease.

It may be concluded from this table, that the most frequent congenital or infantile hereditary diseases are in order :

Buphthalmia,
Congenital cataract,
Coloboma and microphthalmia,
Retinitis pigmentosa,
Hereditary optic atrophy.

Exact figures for the diseases resulting in blindness after childhood are very difficult to obtain. Here are the results obtained by Waardenburg, and those of the 1925-26 Official German statistics, for comparison.

TABLE 21

Eye diseases	Waardenburg		Official german statistics 1925-26 17,026 cases examined by an ophthalmologist
	Complete blindness 1,444 cases	Incomplete blindness 861 cases	
Congenital blindness	14.1	9.2	10.0
Hereditary optic atrophy	20.5	5.2	24.9
Myopia	13,2	24.5	5.1
Detachment of the retina	—	—	10.5
Retinitis pigmentosa	—	—	3.5
Glaucoma	12.9	4.3	15.1
Juvenile cataract .	—	—	30.0
Senile cataract.. . .	2.8	7.2	

These figures demonstrate that myopia is the principal factor in the etiology of complete, and above all of incomplete post-natal hereditary blindness. The German figure for myopia equals Waardenburg's (13.2), if it is assumed that about two-thirds of the cases of detachment of the retina are myopic. About 1/8 of the cases of blindness are therefore due to myopia. If we assume that 17 % of the cases are congenital, of which half are hereditary, we may conclude that about 7 % of the blind are suffering from congenital hereditary blindness.

Blindness is most often caused by optic atrophy, but it is extremely difficult to determine the part of heredity. In 341 cases of optic atrophy, Waardenburg has been able

to establish the following origins with more or less certainty :

Syphilis, 40 %,
Heredity, 40 %,

Brain diseases, including malformations of the skull, of which some are also hereditary, 20 %.

Waardenburg's figures for the percentage of hereditary cases seem extremely high to me. Undoubtedly, the frequency of hereditary optic atrophy varies in different countries. In England according to Usher, the disease is quite prevalent. It is extremely rare in Switzerland. Waardenburg's statistics omit a number of diseases of the optic nerve resulting from other causes than those he mentions (arteriosclerosis, intoxications, traumatisms, etc.). From my personal observation, the hereditary cases are, at least in Switzerland, much less frequent. I cannot therefore, at least for the time being, admit that a maximum of 15 % of the cases of hereditary blindness, or 3 % of all the cases of blindness are due to this cause.

The statistics do not enable us to determine the number of hereditary cases of glaucoma, cataract in adults, and tapeto-retinal diseases.

We can try to estimate the number of hereditary eye diseases.

TABLE 22

APPROXIMATE FREQUENCY OF HEREDITARY EYE DISEASES

Congenital diseases		
Congenital cataract	2 %	7 %
Buphthalmia	1.5 %	
Coloboma and equivalents	1.5 %	
Congenital tapeto-retinal degeneration	1 %	
Various other congenital diseases	1 %	
Myopia		13 %
Optic atrophy		3 %
Retinitis pigmentosa		·3 %
Cataract		7 %
Glaucoma		
Tapeto-retinal diseases		
Total		33 %

We thus obtain an estimate of 33 % of cases of hereditary blindness, which corresponds to that of Waardenburg and von Verschuer.

As we have just said, the frequency of the different hereditary diseases is not the same in all countries. Leber's

disease is most frequent in England and Japan, and quite rare on the continent.

Buphthalmia seems to be more frequent in Holland, Germany and Switzerland, than in America.

Congenital cataract is common in America, Germany, Holland and Switzerland, while in England, according to Usher, zonular cataract is commoner. These variations hold not only for different countries, but for different regions of the same country.

Some years ago, the physicians were trying to establish a relationship between geographical conditions and disease. This problem should also be investigated in ophthalmology, for the number of hereditary diseases varies widely from one country to another. At the present time, it is almost impossible to quote statistics on the relation between the number of hereditary diseases and geographical conditions.

F. — Relation between the incidence of hereditary diseases and sex

It was Waardenburg who first insisted upon the fact that not only in the sex-linked recessive diseases, in which according to the formulae, males should be more often diseased than females, but also in the simple recessive diseases there were more males than females diseased.

I have been able to find the following figures in the literature for the relation between men and women patients with recessive diseases.

TABLE 23

Disease	Author	Ratio		
		Male		Female
Albinism	Waardenburg.	1.75	:	1
	Waardenburg.	1.62	:	1
Total colour blindness	Waardenburg.	1.27	:	1
	Peter.	1.5	:	1
Buphthalmia	Waardenburg.	2.35	:	1
	Kestenbaum.	1.64	:	1
Retinitis pigmentosa (recessive variety)	Nettleship.	1.63	:	1
	Wibaut	1.35	:	1
	de Wilde.	1.5	:	1
	Julia Bell.	1.25	:	1

Several theories have been advanced to explain the preponderance of male subjects and the discrepancy with the theoretical ratio of 1 : 1.

Waardenburg has found a ratio between males and females of 1.05 : 1 in 110 cases of dominant hereditary diseases (aniridia, congenital cataract, microphthalmia, and coloboma). The difference from the theoretical ratio is insignificant.

For comparison, I have calculated the ratio between males and females in Cunier and Nettleship's large pedigree for congenital night-blindness. The ratio is 53.7 % : 47.3 % ± 4.3 %, or 1.11 : 1. The discrepancy is insignificant if account is taken of the mean error.

It appears, therefore, that in dominant diseases the theoretical proportion is attained in practice.

G. — Relation between the incidence of dominant and recessive diseases

We know almost nothing about the relation between the incidence of dominant and recessive diseases. It is obvious that the frequency depends upon the diseases reported in the statistics. Ordinarily, dominant diseases are less serious than recessive.

In 340 cases of congenital hereditary blindness, Hirsch observed 15 cases of direct, or probably dominant, heredity, and 82 cases with collateral, or probably recessive, heredity. The ratio between the two modes is therefore 1 : 5.5.

Fleischer is also of the opinion that recessive diseases are far more frequent than dominant ones. Waardenburg obtained a ratio of 1 : 1.3 in 206 cases of congenital hereditary blindness.

H. — Incidence of hereditary diseases in the descendants of patients suffering from hereditary blindness

The probability of blindness in the descendants in dominant and sex-linked recessive diseases, may readily be calculated from the formulae discussed in a previous chapter. It is obvious that there must be other diseased individuals in the ascendance, in order to determine the mode of transmission.

What are the probabilities of the descendants being

diseased in recessive or sporadically dominant diseases ? In other words can we make a prognosis for the children of patients whose pedigree is unknown to us. We are, unfortunately, obliged to answer that we have no figures which would permit us to answer this question. It would, however, be extremely valuable to be able to advise persons contemplating marriage, on the basis of accurate statistics.

The psychiatrists are far in advance of the ophthalmologists here. The following table gives the average number of diseased children for certain mental diseases when one or both parents are affected.

TABLE 24

Disease	Children		Total abnormal
	Diseased	Psychopathic	
1. *Schizophrenia (quoted from Ruedin) :*			
1 parent diseased	9-10 %	34-42 %	43-52 %
2 parents diseased	53 %	29 %	82 %
2. *Manic depressive psychoses (quoted from Ruedin) :*			
1 parent diseased	30-33 %	33 %	60-66 %
2 parents diseased	62.5 %	37.5 %	100 %
3. *Congenital debility (quoted from Brugger) :*			
1 parent diseased	41 %		
2 parents diseased	91 %		

In ophthalmology, some figures have been published for the transmission of high myopia. Wilson's paper gives the following figures :

TABLE 25

	Myopic children	Non-myopic children	Mean error
Parents not myopic (1). . . .	25 %	55 %	2.3 %
1 parent myopic	44.4 %	55.6 %	2.3 %
2 parents myopic	100 %		

Wilson's figures correspond closely to those of Jablonski.

The number of diseased children of non-myopic parents must not be compared with that of those who have one

(1) Families with at least one myopic child.

myopic parent. The first figure does not correspond to the general probability of having myopic children, but only applies to families who have at least one myopic child. We can only say, that an individual suffering from high myopia will, on the average, transmit his affliction to 44 % of his children.

The following table may give us some information on the transmission of hereditary eye diseases.

TABLE 26

FREQUENCY OF BLINDNESS IN THE PARENTS, BROTHERS, SISTERS AND CHILDREN OF THE BLIND (QUOTED FROM LEWIS)

One or both parents blind . . .	4.2 %
Brothers and sisters blind . . .	9.7 %
Children blind.	1.7 %

From this table, the following calculation may be made : let us suppose that there are 10 blind for 10,000 population (0.1 %), let us also assume an average of 3 children per family. The probability that a child be blind is 0.1 % × 3 according to this table, or 0.3 %. 1.7 % of the blind have blind children. As we have estimated that one-third of all the blind are so from a hereditary disease, and as it is the latter who transmit blindness to their children, the probability that they have blind children is 1.7 % × 3, or 5.1 %. We may therefore say that the risk of having blind children is at least 17 times greater in individuals suffering from hereditary blindness, than in normal individuals. This figure is certainly too low, for many of the children in these statistics have not attained the critical age. In addition, 4.2 % of the blind have one or two blind parents. This figure will be 3 times as high, or 12.6 % for patients with hereditary blindness. According to the suppositions made, the probability for a normal individual to have a blind parent is 2 times 0.1 % or 0.2 %. A patient suffering from hereditary blindness has therefore, 60 times as many chances of having a blind parent, as a normal individual. This ratio is not reversible without correction, on account of the variable number of children. The risk that a patient with hereditary blindness have blind children, may be estimated as 60 times as great as for a normal individual. This figure is certainly closer to the reality than that of 17 % given a while ago.

All these calculations are obviously only of relative value. My purpose was rather to show how the necessary

calculations should be made, had we complete statistics and not approximate estimates, in order to advise persons contemplating marriage, than to arrive at necessarily arbitrary conclusions. Let us hope that it will be possible, in the near future, to base our counsels upon statistics of this type.

III. — THE SOCIAL CONSEQUENCES OF BLINDNESS

The social consequences of blindness may be considered from the point of view of the blind individual, and from a general point of view.

A. — Social consequences for the blind individual

I cannot do better than quote the opinion of Waardenburg on this subject. In the report that he has placed at my disposition, he says,

" Most of the blind are of normal intelligence and of high moral principles. It is not their affliction that oppresses them, but the social difficulties it creates. The difficulty they have in gaining a livelihood, their feeling of dependence, and the need to seek relief oppresses them far more than the blindness itself. "

The social position of the blind and partially blind does not depend only on their eye condition, but upon a series of factors of which the following are the most important :—

1. The social position of the parents.
2. The hygienic and medico-social measures (relief, pensions, etc.).
3. The individual constitution.
    a) The presence of disease of other organs (malformations, mental and brain diseases, deaf-mutism, etc.).
    b) The intellect.
    c) The character and will.
4. The education and training.
5. The age at which blindness appeared.
6. The duration of the blindness.

The social position of the blind is given in an investigation of Waardenburg. He found that of 2,305 blind and amblyopic 14.3 % were of well do to parents, and 85.7 %

of indigent parents. To draw conclusions from these figures, it would be necessary to know the percentage of well to do people in the population. Waardenburg gives no information on this point, nor does he separate the hereditary from the other cases.

The social measures in force in the different countries are obviously of capital importance for the physical and moral well being of the blind. Under this heading must be considered not only the financial relief given to the blind in certain countries (England, Germany, etc.) but what is more important, the provisions for the education of the blind. The institutions for the blind are obviously very useful, all the more so because they train their inmates in a trade. The rational organisation of the societies for the welfare of the blind, favours the improvement of their social status. It is obviously necessary to make the instruction of blind children compulsory, which is not the case to-day in most countries. The creation of classes for the partially blind is obviously a great step forward. Franz von Galeis in 1802 suggested the creation of special sections for the amblyopic in the Vienna homes for the blind. In 1884, Maddox in England suggested the formation of special classes for the partially blind, but it was not until 1907, that B. Harman opened the first school of this type in London. Redslob in 1911 at Strassburg, and Allen in 1913 in Boston founded classes for the amblyopic. To-day, nearly every large city has such classes.

As the partially blind can rarely continue their studies in the ordinary higher schools, it would be useful to add shops for trade training to these schools. To our knowledge, this has already been done in America.

I agree with Waardenburg, that too many partially blind are in institutions for the blind. From a social point of view, the blind and partially blind require an entirely different training. It has been shown, that with a proper training, the partially blind may lead almost normal lives (Voss).

In small towns and rural communities, it is difficult to establish classes for the partially blind. There are usually 10-12 pupils in a class, which corresponds to a total of 10,000-12,000 school children, and a population of 100,000-120,000. In sparsely populated districts, the amblyopic follow the ordinary classes, or are placed in an institution for the blind. Either procedure is disadvantageous for them. The solution would be to create special sections for the partially blind of small towns and rural districts

in the institutions for the blind. Unfortunately, the parents are often unwilling to place their children in such institutions, and for the moment there is no prospect of enacting laws which would make it compulsory.

We shall return to the social workers, who are the precious auxiliaries of the ophthalmological out-patients' departments.

The inferiority of some of the blind is aggravated by the coexistence of diseases of other organs. The mental diseases are the most important. Graseman has found from 10 to 20 % of abnormal children among the inmates of homes for the blind. Waardenburg has observed 10 cases (23 %) of mental debility among 53 partially blind.

The age at which blindness appears is very important. Young subjects adapt themselves more readily than adults. The same holds for the partially blind, who when they are suffering from a congenital or juvenile disease succeed in practising trades for which good vision at first seems indispensable.

B. — The general consequences of blindness

1. *The financial problem*

For the state, the problem of the blind is above all a financial one. The state must make the following expenditures for the blind :—

a) The instruction and training,
b) The creation of homes for the blind,
c) The relief of the indigent blind,
d) The subsidies to works in favour of the blind (libraries, journals, lectures, legal aid, etc.).

According to Clausen, the cost of training the blind and deaf and dumb is twice as high as that for normal children. Kaiser says that in Germany blind children cost the government 1,500 R.M. per annum, and the partially blind 450 R.M. These sums are even greater in America. It is estimated that an inmate of a home for the blind costs 700 dollars per annum, and a pupil of a class for the partially blind 450 dollars.

In France, according to Lewis, the annual expenditure for a pupil of a class for the amblyopic is twice as great as for a normal pupil. He gives the following figures, about 500 francs per annum for a normal pupil, and 1,000 francs

for a pupil of a special class. The difference is even greater in the higher schools.

One-fifth of the inmates of the homes for the blind in Germany are amblyopic according to Sexe. Several authors have claimed that economies could be realised by the creation of more classes for the amblyopic. It must not be forgotten that many of these amblyopics come from villages where there are not enough pupils to form a class. I think, apart from the financial considerations, that special divisions of the amblyopic should be created in these institutions, in view of the necessity of separating the blind from the amblyopic.

2. *The eugenic problem*

In my opinion, eugenics is principally important in the progressive hereditary diseases. The progression of these diseases is due to the fact that the affected subjects are more prolific than normal individuals. This is particularly the case for patients suffering from mental debility. The weak-minded in Munich have 64 % more children than normal individuals according to von Verschuer. In Berlin, the weak-minded have 4 children per family where the normal average is 2. In Stuttgart, only the weak-minded have an excess of births over deaths. This is not the case for the blind. The blind marry more rarely than the normal, and seem to be less prolific. According to the German statistics for 1925, the number of unmarried blind between the ages of 40 and 50 is distinctly larger than for normal individuals. Among the blind, 53 % of the men were bachelors, and 27.7 % of the women spinsters, as compared with 10.6 % and 6.7 % among normal men and women respectively. Between the ages of 40 and 50 then, the blind are unmarried 5 times as often as the normal individuals. In addition to this, there is a high infant mortality among the subjects to certain of the hereditary eye diseases. Very often too, these patients have no children at all. This is due to the fact that the modified genes carry lethal or sub-lethal factors.

I am entirely in accord with Waardenburg, that the eugenic measures must be considered not only from the social angle, but also from a purely humanitarian one. As physicians, our duty is to prevent and cure disease. It is logical then, that from the ophthalmological standpoint, we consider all the possible steps which may prevent hereditary eye diseases. Our conceptions of eugenics may differ.

Some may be interested only in improving the race, and others in an individual and humanitarian objective. In practice, whatever our conceptions, our purpose will always be to reduce the number of blind with hereditary eye diseases. We shall therefore consider the measures which may be proposed to serve this end in the next chapter.

IV. — THE MEASURES WHICH MAY BE PROPOSED TO REDUCE THE NUMBER OF BLIND WITH HEREDITARY EYE DISEASES

To reduce the number of blind with hereditary eye diseases, it is necessary to prevent blindness in these diseases, and the transmission of the diseases.

A. — Measures to ameliorate or cure the morbid condition in patients with hereditary diseases

1. *Purely medical measures*

If it is recalled that the hereditary diseases are ordinarily refractory to all medical treatment, it may appear useless to attempt to prevent blindness in hereditary eye diseases. This nihilism is erroneous. There are a number of hereditary eye diseases in which judicious treatment may improve the morbid condition, and very often prevent blindness.

The means at our disposal for dealing with the congenital malformations (microphthalmia, etc.) are very restricted. In congenital cataract, surgical intervention may be considered. In spite of the operation, sight often remains insufficient because of the aplasia of the macula. This same aplasia plays a large role in albinism, in which we succeed in reducing the photophobia by tatooing. Buphthalmia can very often be definitively cured.

Therapeutic measures are ordinarily futile in the abiotrophies of the retina. Endocrine treatment, and operation on the sympathetic, however, seem to succeed in certain cases. The modern treatment of detachment of the retina in myopia may be cited as an example of the progress made in the treatment of hereditary diseases.

2. *Hygienic and medico-social measures*

There are certainly less blind with hereditary diseases in those countries where the possibilities for appropriate medical treatment, free medical advice and hospitalization are at the disposition of the public. The number of hereditary blind may be further reduced, even in these countries, in my opinion. The social workers attached to the large ophthalmological clinics and out-patients' departments may accomplish this. The importance of the social worker has been understood in America, but continues to be underestimated in Europe. The social worker visits the diseased, impresses, the necessity of submitting to medical treatment which may prevent blindness, upon them, and investigates their social status and the means of aiding them. For patients living at great distances from the oculist, this is particularly important. From the purely social standpoint, the social worker is invaluable, for he may undertake the necessary steps to institutionalize the patient, secure a training in a suitable trade for him, etc.

The societies for the welfare of the blind also do these things, but it is often very difficult for them to reach all the blind, who very often do not make themselves known, nor are they familiar with the medical measures which may attenuate the patient's disease.

The addition of social workers to the staffs of the ophthalmological out-patients' departments is one of the principal steps to be taken to reduce the number of blind with hereditary diseases, in my estimation.

Hygienic measures have principally been considered for dealing with myopia. The opinions on the importance of the exogenous factors in this disease vary widely. Some believe that the disease is solely due to exogenous causes, others attribute more or less importance to them, and still others consider that heredity plays the principal, if not the only, part. In my opinion, none of the evidence cited in favour of the exogenous origin of myopia is convincing. I do not believe, therefore, that the schools for myopics can arrest the progress of the disease or its serious consequences. I do consider these special schools very important for the appropriate instruction and training in trades which they give to these subjects.

B. — Measures to prevent the transmission of hereditary eye diseases leading to blindness

1. *Theoretical measures*

It is obvious that by preventing the carriers of pathological genes from having children, the number of blind with hereditary eye diseases may be reduced.

Nevertheless, even from a theoretical point of view, there are considerable difficulties. Indeed, the external manifestation of recessive genes is only present in the men subject to sex-linked recessive diseases, and in some of the heterozygous women.

In digeneticism, and in irregular dominance, the genotypically diseased individual is often phenotypically sound.

If one wishes to prevent procreation in all the carriers of morbid genes, it is necessary to include individuals who may be normal. Theoretically, then, it is necessary to prevent reproduction in

a) the patients in regular dominance;
b) the patients, their brothers, and sisters, and even the children of the latter in irregular dominance;
c) the patients, their children, and their brothers, and sisters in recessivity;
d) the patients and all their sisters and daughters in sex-linked recessivity;
e) the patients, their children, their brothers and sisters (and eventually their children), in digeneticism.

Another difficulty arises from the fact that the hereditary diseases often manifest themselves only after puberty. As a result, the patient may already have transmitted his affliction when the disease first manifests itself. In families with late manifestation of dominant diseases, it would be necessary to prevent procreation in all the patients' children.

It is not without interest to discuss the question of consanguinity from the theoretical point of view. Consanguinity favors the manifestation of recessive diseases. By the mating of two heterozygotes, we are enabled, in theory at least, to recognize the carriers of these diseases, and to prevent them from procreating, thereby diminishing the number of carriers. Paradoxical as it may seem then, consanguinity is to be recommended in theory. This conclusion is only valid where consanguinity has no other consequences than the manifestation of recessive genes. We have already shown, however, that certain latent genes

may become manifest as the result of repeated consanguinities in the ancestry. It may be then questioned whether consanguinity does not have an influence on the genotypic constitution of the individual which stimulates the manifestation of otherwise latent genes.

2. *Practical measures*

An abyss separates the theory from the practice. It is obvious that it is quite impossible to prevent reproduction in all the carriers of pathological genes.

We are concerned here with the possibility of realizing these measures at the present time. Our success in reducing the number of hereditary blind will depend above all on the general education in the facts of heredity. The physicians and oculists, above all, should be acquainted with the necessary measures. It is only with their support, that we can hope to interest the authorities and the public.

I. — *Education in the facts of heredity.*

The physicians and especially the oculists, do not, unfortunately, take sufficient interest in the problems of heredity. Special courses in biology, with particular stress on the importance of heredity should be planned for medical students and practitioners.

Difficulties arise from the fact that, in ophthalmology for instance, special training is necessary in order to be able to apply the laws of heredity to eye diseases. Very often, the ophthalmologist is unfamiliar with the principles of heredity, and the genetic expert with ophthalmology. Collaboration is essential. It is important that the oculist be familiar with genetic principles, for he is then able to warn the patient against the danger of transmitting a hereditary disease, and to properly report his observations.

I draw special attention to the necessity of examining the fundus oculi by light from which the red has been filtered. It is only in such light, that many hereditary eye diseases can be properly recognized. Many cases of nystagmus, amblyopia, etc. are accompanied by an aplasia of the macula which can only be seen in this light.

The oculists often consider as hereditary only those cases in which other members of the family are, to their knowledge, diseased. This conception is a mistaken one, as

we have already pointed out, for many sporadic cases are also hereditary.

If we wish to reduce the number of blind, we must furnish the authorities with convincing evidence of the necessity of the measures we propose.

At the present time, the public is insufficiently interested in heredity. This lack of interest is probably due to ignorance. We must popularize the knowledge of genetics by expanding the teaching of biology in the higher schools, and by night courses for adults.

Special emphasis must be placed upon consultation by persons contemplating marriage. The existing facilities for such consultations must be extended, and the public made to understand the importance of the information thus obtained. The Prevention of Blindness Committee of the Union of Counties Associations for the Blind, has made certain recommendations :

" A member of a stock, in which there is definitely inheritable disease causing blindness, even if the disease is not manifest in his or her case, should be strongly urged to consult an ophthalmologist who, with the assistance of a pedigree, would advise as to abstention from parenthood. "

" A blind person contemplating marriage should seek the advice of a competent ophthalmologist who will no doubt obtain a pedigree and, if necessary, consult a genetic expert. "

In my opinion, these rules may be completed by insisting upon the dangers of consanguinity, and in recommending that the consultant draw special attention to this point.

The pre-marital consultations are usually concerned with general diseases. An oculist competent in genetics should also be called in consultation. The offices for pre-marital consultation should have social workers attached to them to investigate the consultee's genealogy where necessary. It is obvious that this can hardly be done in the present hard times. The pre-marital certificate should be made obligatory.

In Germany, the subsidies to newly married couples are only granted if a pre-marital certificate has been obtained.

According to P. Lewis, the American Committee for the Prevention of Blindness proposed a law making the pre-marital certificate obligatory which was defeated in the New York State Legislature. The other states have also failed to enact this legislation.

Ordinarily, the blind gladly follow the advice given them. It should be relatively easy to make them understand the importance of not having children.

II. — *The improvement of the statistics.*

In a previous chapter, we have drawn attention to the imperfections of the statistics. As we have pointed out, we know neither the incidence of hereditary blindness, nor that of the different hereditary eye diseases.

To improve the statistics, we must proceed as follows :

A. *Improve the classification.*

a) by establishing an international unified classification,
b) by clearly separating hereditary and non-hereditary cases,
c) by having the patient examined by oculists competent in genetics.

B. *Improve the litterature.*

I can only reiterate the recommendations of Julia Bell (1933) who urges the importance of,
a) providing sufficient clinical details of cases to enable readers of a future generation to be quite sure of the diagnosis,
b) collecting as complete pedigrees as possible,
c) complete examination of all the members of the family, including the unaffected ones, as the latter often present abortive eye diseases, or diseases of other organs which may be considered as equivalent,
d) the publication of single-case histories with their pedigrees,
e) the publication of anomalous pedigrees.

The improvement of the statistics has more than a mere theoretical importance. It is of capital practical importance. It is only when we possess good statistics, that we shall be able to make an exact prognosis for the diseased individual's offspring.

Von Verschuer has proposed the creation of special institutes for the study of human genetics. I believe that the work of the scientific societies as they exist to-day in England, America, and elsewhere is adequate for the present.

C. *Organization of a register for each country.*

To determine whether there were cases of hereditary eye diseases in an individual's ancestry, it would be invaluable

to be able to consult a central register accessible only to physicians. The ophthalmologists would make a detailed report of every blind person (nature of eye disease, general diseases, pedigree, etc.). It is obvious that such a register would only become useful after a number of years, and that its creation is now beset with difficulties. In the meanwhile, recourse might be had to private bodies to keep the register. The ophthalmologists and school physicians would be required to report all hereditary and sporadic cases. A central institution for the collection of case histories of hereditary diseases already exists in America. The establishment of a general register has been proposed in Germany. The 1933 report of the Prevention of Blindness Committee contains a model form of report containing all the questions which may be of interest for the statistics. I think the English form of report might serve as an example, for the information demanded about the family of the patient is most detailed. In certain countries, there is a register of school children. The histories of the children with eye diseases might serve as the foundation for the register we propose.

In England, the institutions for the blind make a detailed report of the examination of the patient and note whether there are any hereditary diseases in the family, and whether marriage may be considered.

III. — *Measures to prevent the transmission and appearance of hereditary eye diseases.*

A. *Diminution of consanguineous marriages.*

The opinion of many oculists that consanguinity is not dangerous when there are no hereditary diseases in the ancestry is a mistaken one as we have already shown. The oculists and public must be convinced of the dangers of consanguinity, even in unions between second and third cousins.

In Belgium, marriage between first cousins is forbidden by the civil code. Until 1918, marriages between the children of first cousins were also forbidden.

In other countries, marriage between first cousins is generally not illegal. The canon law forbids such marriages, but dispensations may be had.

B. *Diseases in which procreation must be prevented.*

1. *Cases in which it is absolutely necessary to prevent transmission*

a) Patients with serious dominant diseases.

The most important diseases in this class are,
congenital cataract,
aniridia,
microphthalmia (dominant type),
retinitis pigmentosa (dominant type),
glioma,
(eventually, congenital optic atrophy).

b) Patients with concomitant hereditary diseases of other organs.

The transmission of eye diseases is particularly to be apprehended in cases where there are concomitant hereditary diseases of other organs, particularly mental debility, deaf mutism, or nervous or mental diseases. In my opinion, procreation must be prevented even in sporadic cases of this type.

c) Patients with sporadic dominant diseases, or who have affected children.

This recommendation corresponds to that of the Prevention of Blindness Committee.

d) Normal patients who have more than one child with hereditary eye disease (recommendation of the Prevention of Blindness Committee).

This case arises principally for the recessive diseases, of which the most frequent are,
buphthalmia,
retinitis pigmentosa (recessive type),
total colour blindness.

c) The sisters of patients with sex-linked recessive diseases.

It is principally to Leber's disease, that this measure is applicable. The recommendation of the Committee that the sisters of affected males abstain from parenthood, in all but sporadic cases, seems justified to me, as well as the opinion that there is no risk to the descendants of the affected men, except in those families in which transmission by the male has occurred.

2. *Cases in which abstention from parenthood is to be recommended.*

a) Cases of serious recessive diseases.

As the children of these patients are ordinarily unaffected, it is difficult to demand abstention from parenthood, at least for the present.

The difficulties are particularly great for the relatively frequent diseases like myopia. Despite the fact that myopia is the most frequent cause of hereditary blindness, the attempt to prevent its transmission would lead us too far afield.

The only thing we can do at present, is to advise a patient with high myopia not to marry a person similarly affected, for then 100 % of the children will be myopic.

b) Carriers of serious recessive diseases.

Wegner (1934) proposed the prevention of parenthood in the children and even in the sisters of patients with serious recessive diseases. I do not think it possible to go so far.

I do not concur in the opinion of Fleischer (1934) who believes that in families practising trades calling for perfect sight (sailors, painters, dyers, hunters) the transmission of anomalies of colour vision may be prevented by eugenic measures.

C. *Application of the measures to prevent the transmission of blindness.*

1. *Celibacy.*

The necessity for celibacy in hereditary blindness must be explained early in the schools for the blind.

It must be recalled that the blind often show a lack of understanding and marry other blind individuals. It is apparent that the offspring of such marriages run a greater risk of being blind (sometimes even 100 %).

In England, the blind may earn their living in the private institutions only so long as they remain celibate (1).

Even if the blind do not marry, there is always the possibility of natural children, and the transmission of the disease.

Birth control which is practised in England, also proposes

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(1) Recently the married blind have been permitted to continue to work, if they submitted to sterilization.

to prevent the transmission of hereditary diseases by attempting to prevent the increase in the number of children in poor families, particularly where there is danger that the children be deficient. It is hoped thereby to lighten the financial burden of these families and permit the parents to take better care of a smaller number of children (1).

2. *Segregation*

It has also been suggested that the blind be segregated like the insane, in order to prevent their reproduction.

Such a practice, which would entail enormous expense, is inhuman, for the blind are of normal intelligence and morality.

It is true that some of the blind are in homes, but this is due rather to the social difficulties they encounter. It is only for the blind with mental diseases that segregation is necessary.

3. *Sterilization.*

Sterilization is undoubtedly the best method for preventing the transmission of hereditary blindness, particularly as the procedures of vasectomy and salpingectomy are now without danger.

a) *Voluntary sterilization.*

The great advantage of voluntary sterilization is that in leaving the decision to the patient, there is no implication of moral inferiority. It is obvious that an educational campaign among the blind must be organized to explain the necessity of sterilization. Special committees exist in England to study eugenic problems. According to Usher, sterilization has been practised in several cases of hereditary blindness, and in individuals with one or more children with hereditary eye diseases. In the United States, it seems that a patient may have himself sterilized if he so desires (2).

It must not be forgotten that in certain countries, like Switzerland, Italy, etc., sterilization for eugenic reasons is not authorized. It is principally in these countries that a

(1) Euthanasia recently proposed by Bickerton for serious malformations has small chance of being accepted by our generation.

(2) According to Park Lewis special laws authorizing voluntary sterilization have been proposed.

campaign in favour of voluntary sterilization must be organized, for it is our most effective weapon against hereditary blindness.

Needless to add, sterilization should be available gratis to indigent patients.

b) Obligatory sterilization.

It is apparent that sterilization is essential in the serious mental diseases. According to Park Lewis, 30 of the 48 United States have passed laws making sterilization compulsory for criminals, and in certain mental diseases. The hereditary diseases of other organs are not included, despite the recommendations of the eugenics committees (1).

In Germany, the law of July 14 th, 1933, makes compulsory the sterilization of all individuals with serious diseases which according to medical knowledge have a great possibility of resulting in deficient offspring (congenital mental debility, Huntington's chorea, hereditary deafness, hereditary blindness, serious malformations, and alcoholism). This law does not apply to drug addicts, nor to apparently normal individuals with one or more children with manifestly hereditary diseases.

The law makes no distinction between the different modes of transmission, or between the various eye diseases causing blindness. The sterilization may be demanded by the patient himself, by the spouse *in loco parentis*, by the government's physician, or by the director of the hospital, asylum, reformatory, or prison in which the patient is confined. All the cases are submitted for judgement to a sanitary council made up of a judge, a government physician, and a practising physician. The patient may appeal the decision to a special court which has final jurisdiction. Wegner (1934) believes that 30 % of the cases of blindness may be prevented thanks to this law. There are, however, in my opinion, certain disadvantages to compulsory sterilization. The main one to be feared is that the patient apprehensive of being declared to the competent authority have recourse to the physician as infrequently as possible, and furnish him with an inexact history, thereby rendering the physician's task more difficult, and preventing him from properly treating certain patients.

(1) In Switzerland, only the law of the Canton of Vaud permits sterilization in mental diseases recognized as incurable and certain to be transmitted to the offspring.

CONCLUSIONS

In conclusion, we shall briefly summarize the measures discussed in detail in the previous chapters, which we believe will enable us to diminish the incidence of hereditary blindness.

A. — Collection of precise and complete statistics,

B. — Training of physicians (especially of ophthalmologists) in genetics, and education of authorities and public,

C. — Extension of facilities for pre-marital consultation, and the general introduction of the pre-marital certificate,

D. — Increased use of social workers,

E. — Decrease in consanguineous marriages,

F. — Decrease of the transmission of hereditary eye diseases by making sterilization available to the patients.

I am of the opinion that a committee should be named to study the means of realizing these different objectives. In working upon an international plane, this committee should be able to bring together the material which will permit judgement of the efficacity of the steps taken to decrease hereditary blindness in the various countries, and concrete recommendations to be made in the near future.

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